

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyoxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $\text{NR}^{13}\text{R}^{14}$, CO_2R^{13} , $\text{O}(\text{C}=\text{OR}^{13})$, SO_2R^{14} , SOR^{14} , $(\text{C}=\text{O})\text{NR}^{13}\text{R}^{14}$, or $\text{NR}^{14}(\text{C}=\text{O})\text{R}^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_3\text{-C}_6$ alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, $\text{C}_1\text{-C}_4$ alkyl and benzyl;

(ii) an oligopeptide of 1 to 5 amino acids or a peptidomimetic molecule having substantially similar binding properties as the oligopeptide;

(iii) $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_6\text{-C}_{10}$ bicycloalkyl, $\text{C}_3\text{-C}_7$ cycloalkylmethyl, or $\text{C}_7\text{-C}_{10}$ arylalkyl, which may be additionally substituted with R^{11} as defined above;

R_3 is selected from the group consisting of:

(i) hydrogen, phenyl, hydroxyl, $\text{C}_1\text{-C}_{12}$ hydrocarbon chain or $\text{O-C}_1\text{-C}_{12}$ hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl and NHR^{11} , wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

(i) hydroxyl, amino, carbamido, carbamyl, carbamyoxy or halogen;

(ii) hydrogen; and

(iii) $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkenyl, $\text{C}_3\text{-C}_7$ cycloalkenyl, or $\text{C}_1\text{-C}_3$ alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) hydroxy, halogen, $\text{C}_1\text{-C}_4$ haloalkyl, or $\text{C}_1\text{-C}_4$ haloalkoxy;

(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, $C_1[.]$ - C_3 alkylsulfonyl, or sulfone; and

(iii) $C_1[.]$ - C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above; and

(iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;

alternatively Z' and R_1 collectively form a ring system selected from the group consisting of:

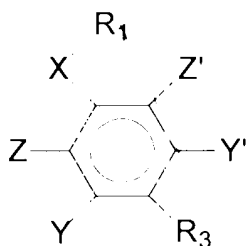
(a) C_5 - C_8 carbocyclic ring which may be saturated or unsaturated, and which may be additionally substituted with at least one R^{11} as defined above; and

(b) C_5 - C_{10} heterocyclic ring system which may be saturated or unsaturated and which includes at least one nitrogen, oxygen or sulfur atom, and which may be additionally substituted with at least one R^{11} as defined above;

and pharmaceutically acceptable salts thereof; with the proviso that when $X-R_1$ is a fluorinated keto acyl, Z is hydrogen.

12. (Once Amended) [The] A method [of] according to claim 8, wherein the picornavirus species is a rhinovirus species.

13. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species,] inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is $-C=O$;

R_1 is $-CF_3$;

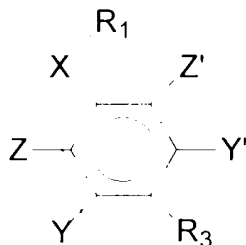
Z and Z' are hydroxyl, except when $X-R_1$ is a fluorinated keto acyl group, Z must be hydrogen;

R_3 is hydrogen; and

Y and Y' are selected from the group consisting of $-Cl$, $-I$, $-Br$, $-CF_3$, $-F$, $-CN$, $-COOH$, $-SO_3H$, $-SO_2NH_2$ and $-CONH_2$; and

and Z' and R_1 cannot form a ring.]

14. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species.] inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is $-\text{C}=\text{O}$;

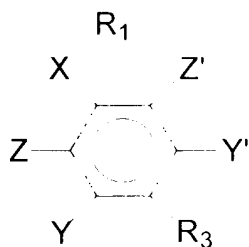
R_1 is $-\text{CF}_3$;

Z is hydroxyl, except when $\text{X}-\text{R}_1$ is a fluorinated keto acyl group, Z must be hydrogen;

Z' and R_3 are hydrogen; and

Y and Y' are selected from the group consisting of $-\text{Cl}$, $-\text{I}$, $-\text{Br}$, $-\text{CF}_3$, $-\text{F}$, $-\text{CN}$, $-\text{COOH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{NH}_2$ and $-\text{CONH}_2$ [; and
and Z and R_1 cannot form a ring.]

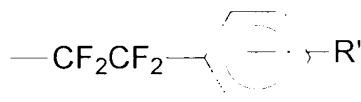
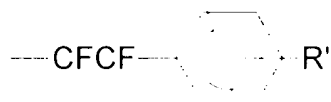
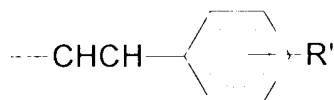
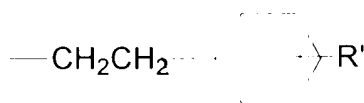
15. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species.] inhibiting picornaviral replication in a subject, wherein said compound



has the formula:

wherein X is $-\text{C}=\text{O}$;

R_1 is H, $-\text{CH}_3$, $-\text{CF}_3$, $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, CH_3-CH_2- , $\text{CH}_3-\text{CH}_2-\text{CH}_2-$, $\text{CF}_3-\text{CF}_2-\text{CF}_2-\text{CF}_2-\text{CF}_2-$, $-\text{NH}-\text{R}''$ or one of the following phenyl groups



wherein R' is -OH, -NH₂, -COOH, or -COCH₃ and R'' is -OH, -NH₂, -OCH₃ and -OCH₂CH₃;

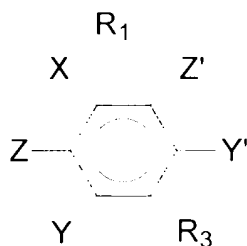
Z and Z' are hydroxyl, except when X-R₁ is a fluorinated keto acyl group, Z must be hydrogen;

R₃ is hydrogen; and

Y and Y' are -CF₃ [; and

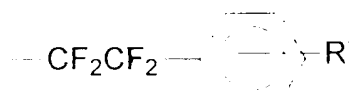
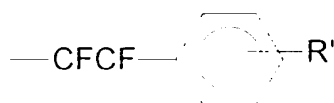
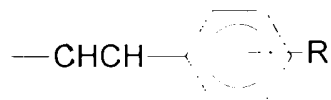
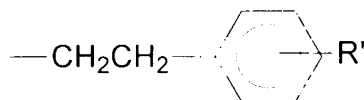
and Z' and R₁ cannot form a ring.]

16. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species.] inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is -C(=O)-;

R₁ is H, -CH₃, -CF₃, CH₃-CH₂-CH₂-CH₂-CH₂-, CH₃-CH₂-, CH₃-CH₂-CH₂-, CF₃-CF₂-CF₂-CF₂-CF₂-, -NH-R'', or one of the following phenyl groups



wherein R' is $-OH$, $-NH_2$, $-COOH$, or $-COCH_3$ and R'' is $-OH$, $-NH_2$, $-OCH_3$ and $-OCH_2CH_3$;

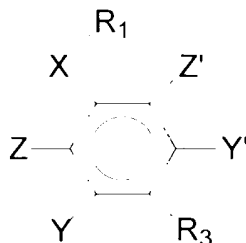
Z is hydroxyl, except when $X-R_1$ is a fluorinated keto acyl group. Z must be hydrogen;

Z' and R_3 are hydrogen; and

Y and Y' are $-CF_3$; [; and

and Z' and R_1 cannot form a ring.]

17. (Once Amended) A method [for the treatment of a disease caused by a picornavirus species.] of inhibiting picornaviral replication in a subject, wherein said [compound has] method includes the use of a compound with the formula:



X is selected from the group consisting of $-C=O-$, $-S=O-$, and $-C=S-$;

R_1 is selected from the group consisting of:

(i) a hydrocarbon chain which may be unsubstituted or substituted with at least one R^{11} , wherein R^{11} is selected from the group consisting of:

(ia) C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamoyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $NR^{13}R^{14}$, COR^{13} , $O(C=OR^{13})$, SO_2R^{14} , SOR^{14} , $(C=O)NR^{13}R^{14}$, or $NR^{14}(C=O)R^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1 - C_6 alkyl, and C_3 - C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, C_1 - C_4 alkyl and benzyl;

R_3 is selected from the group consisting of:

(i) phenyl, hydroxyl, C_1 - C_{12} hydrocarbon chain and O - C_1 - C_{12} hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl, and NHR^{11} , wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

(i) hydroxyl, amino, carbamido, carbamyl, carbamyl, carbamyl, and halogen;

(ii) C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_3 - C_7 cycloalkenyl and C_1 - C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) halogen, C_1 - C_4 haloalkyl, and C_1 - C_4 haloalkoxy;

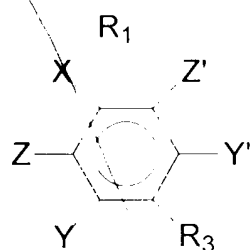
(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, C_1 - C_3 alkylsulfonyl, and sulfone; and

(iii) C_1 - C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above; and

(iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;

and pharmaceutically acceptable salts thereof; with the proviso that when $X-R_1$ is a fluorinated keto acyl, Z is hydrogen.

18. (New Claim) -- A method of inhibiting picornaviral replication in a subject, comprising the step of administering an effective amount of a compound having a formula:



wherein

- 5 X is selected from the group consisting of C=O, S=O, C=S, (C=O)-NH, (C=O)-O and (C=O)-S:

R₁ is selected from the group consisting of:

- 10 (i) hydrogen, hydroxyl or a hydrocarbon chain [of] from [about] 1 to about 10 carbons long selected from the group consisting of saturated, unsaturated and fluorinated, wherein said hydrocarbon chain is unsubstituted or substituted with at least one R¹¹, wherein R¹¹ is selected from the group consisting of:

(ia) C₁-C₄ alkyl, C₂-C₄ alkenyl, C₃-C₈ cycloalkyl, C₆-C₁₀ bicycloalkyl or aryl which may be substituted or unsubstituted;

15 (ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamoyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

20 (id) NR¹³R¹⁴, CO₂R¹³, O(C=OR¹³), SO₂R¹⁴, SOR¹⁴, (C=O)NR¹³R¹⁴, or NR¹⁴(C=O)R¹³;

wherein:

25 R¹³ is selected from the group consisting of hydrogen, phenyl, benzyl, C₁-C₆ alkyl and C₃-C₆ alkoxyalkyl; and

R¹⁴ is selected from the group consisting of hydrogen, hydroxyl, C₁-C₄ alkyl and benzyl;

30 (ii) an oligopeptide of 1 to 5 amino acids or a peptidomimetic molecule having substantially similar binding properties as the oligopeptide:

(iii) C₃-C₆ cycloalkyl, C₆-C₁₀ bicycloalkyl, C₃-C₇ cycloalkylmethyl, or C₇-C₁₀ arylalkyl, which may be additionally substituted with R¹¹ as defined above;

35 R_3 is selected from the group consisting of:

(i) hydrogen, phenyl, hydroxyl, C_1 - C_{12} hydrocarbon chain or O - C_1 - C_{12} hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

40 (ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl and NHR^{11} , wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

45 (i) hydroxyl, amino, carbamido, carbamyl, carbamyoxy or halogen;

(ii) hydrogen; and

(iii) C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_3 - C_7 cycloalkenyl, or C_1 - C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

50 (i) hydroxy, halogen, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, or hydrogen except that Y and Y' cannot be hydrogen simultaneously;

(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, C_1 - C_3 alkylsulfonyl, or sulfone; and

55 (iii) C_1 - C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above; and

(iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;

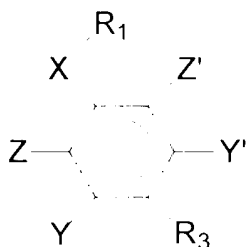
alternatively Z' and R_1 collectively form a ring system selected from the group consisting of:

(a) C_5 - C_8 carbocyclic ring which may be saturated or unsaturated, and which may be additionally substituted with at least one R^{11} as defined above; and

60 (b) C_5 - C_{10} heterocyclic ring system which may be saturated or unsaturated and which includes at least one nitrogen, oxygen or sulfur atom, and which may be additionally substituted with at least one R^{11} as defined above;

and pharmaceutically acceptable salts thereof; with the proviso that when X - R_1 is a fluorinated keto acyl, Z is hydrogen.

19. (New Claim) -- A method of inhibiting picornaviral replication in a subject, wherein said method includes the use of a compound with the formula:



X is selected from the group consisting of $-\text{C}=\text{O}-$, $-\text{S}=\text{O}-$, and $-\text{C}=\text{S}-$;

R_1 is selected from the group consisting of:

(i) a hydrocarbon chain which may be unsubstituted or substituted with at least one R^{11} , wherein R^{11} is selected from the group consisting of:

(ia) $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_6\text{-C}_{10}$

bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyoxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $\text{NR}^{13}\text{R}^{14}$, COR^{13} , $\text{O}(\text{C}=\text{OR}^{13})$, SO_2R^{14} , SOR^{14} , $(\text{C}=\text{O})\text{NR}^{13}\text{R}^{14}$, or $\text{NR}^{14}(\text{C}=\text{O})\text{R}^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_3\text{-C}_6$ alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, $\text{C}_1\text{-C}_4$ alkyl and benzyl;

R_3 is selected from the group consisting of:

(i) phenyl, hydroxyl, $\text{C}_1\text{-C}_{12}$ hydrocarbon chain and $\text{O-C}_1\text{-C}_{12}$ hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl, and NHR^{11} , wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

- 30 (i) hydroxyl, amino, carbamido, carbamyl, carbamyloxy, and halogen;
- (ii) C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_3 - C_7 cycloalkenyl and C_1 - C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;
- Y and Y' are independently selected from the group consisting of:
- (i) halogen, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, or hydrogen except that Y and Y' cannot be hydrogen simultaneously;
- 35 (ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, C_1 - C_3 alkylsulfonyl, and sulfone; and
- (iii) C_1 - C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above; and
- 40 (iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;
- and pharmaceutically acceptable salts thereof; with the proviso that when X-R_1 is a fluorinated keto acyl, Z is hydrogen. --

REMARKS

Claims 8 and 12-17 are pending in the application. Applicants have amended claims 8 and 12-17, and added new claims 18-19.

35 U.S.C. §112, FIRST PARAGRAPH REJECTION OF CLAIMS 8 AND 12-17

The Examiner has rejected claims 8 and 12-17 on the grounds that they are not enabled by the specification. The Examiner has suggested amendments to these claims to overcome the §112, first paragraph rejections. Claims 8 and 12-17 have been amended according to the Examiner's suggestion. Therefore, it is respectfully submitted that such claims are patentable, having overcome this rejection.